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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
8375-000006/DVA

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On September 10, 2008

Signature

Typed or printed name G. Gregory Schivley / William A. Ziehler

Application Number	Filed
10/652,138	August 29, 2003
First Named Inventor	
Koichiro Tanaka	
Art Unit	**Examiner**
1618	Zohreh A. Fay

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

X

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

X

I am the

☐ applicant/inventor

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 27,382 / 61,415.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Signature

G. Gregory Schivley / William A. Ziehler
Typed or printed name

248-641-1600
Telephone number

September 10, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	10/652,138
Filing Date:	August 29, 2003
Applicant:	Koichiro Tanaka
Group Art Unit:	1618
Examiner:	Zohreh A. Fay
Title:	PHARMACEUTICAL COMPOSITION CONTAINING VISCOELASTIC SUBSTANCE AND MEDICATION
Attorney Docket:	8375-000006/DVA

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

ARGUMENT IN SUPPORT OF PRE-APPEAL BRIEF REQUEST FOR REVIEW

Sir:

Applicant requests review of the Final Rejection mailed June 12, 2008 in the above identified Application. This request is filed along with a Notice of Appeal.

REMARKS

With all due respect, the Examiner has ignored the method limitations of the pending claims and improperly examined this application as containing only composition claims. For purposes of this appeal, APPLICANT ADMITS THAT THE COMPOSITION IS OLD. He instead claims a new use of an old substance.

Claims 23-31 and 33-43 are pending in the application and stand finally rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Viegas et al. (U.S. Pat. No. 5,587,175) in view of Chang (U.S. Pat. No. 6,051,560) and further in view of Christ et al (U.S. Pat. No. 6,254,587). Applicant respectfully submits that these references cannot establish a case of obviousness as the rejection fails to provide an apparent reason for a person of ordinary skill to make the alleged combination. Moreover, Applicant has identified a heretofore unappreciated

problem in the art and provides the present claims as a way to address the problem, which is a recognized indicium of nonobviousness. Applicant has also submitted very probative evidence of important secondary considerations including unexpected results, satisfaction of a long-felt need, and is contrasted by the failure of others. The Examiner did not give proper weight to this evidence.

Background and Summary of Claims

Independent claims 23 and 31 are drawn to methods for preservation and/or treatment against bacterial infection and/or inflammation in an ophthalmological surgery site, and independent claim 39 is drawn to a method for preservation and/or treatment against infection and/or inflammation during cataract surgery. These claims have in common application of a pharmaceutical composition *to an interior portion of the eyeball*. The applied pharmaceutical composition includes a viscoelastic substance and an antimicrobial agent mixed in the viscoelastic substance.

During conventional eye surgery, a viscoelastic substance (without an antimicrobial) is used to prevent collapse of an interior chamber of the eye due to pressure loss caused from outward flowing aqueous humor. There is a chance that an infectious microbe may be introduced into the eye during the surgical procedure. To combat post-operative infection, the prior art teaches to administer an antibacterial agent systemically, either orally or intravenously, or locally (but not to the interior of the eyeball) using an ophthalmic solution. Infection can lead to conditions such as endophthalmitis, involving inflammation of the intraocular cavities (i.e., the aqueous or vitreous humor), and may lead to other complications including blindness. Thus, it is paramount to prevent post-operative infection.

Applicant has unexpectedly identified that the viscoelastic substance itself can actually help cause post-operative infection. When applied within the eye, the viscoelastic substance can enfold (cover) bacteria that are also introduced into the eye during surgery, thereby protecting the bacteria from contact with the separately administered antibiotic. While most of the viscoelastic substance is removed following surgery, residual traces can persist. Protection of bacteria within these traces is compounded by the fact that the half-life of the viscoelastic substance can be several hours. Thus, if a bacterium is enfolded by the viscoelastic substance, systemic or locally applied antibacterial agents cannot reach or contact the bacterium within these residual traces of gel and conventional methods to treat infection may be inadequate.

In recognition and appreciation of this unique and heretofore unknown problem, Applicant devised the present inventive methods that apply a viscoelastic substance with an antimicrobial agent mixed in the viscoelastic substance. Hence, if the viscoelastic substance

introduced during surgery is responsible for the deposition and proliferation of bacteria within the eye, mixing an antimicrobial agent into the viscoelastic substance can prevent the enfolded bacteria from eluding physiological disinfection and sterilization. The present invention therefore presents the antimicrobial agent at the most requisite time and place to prevent infection by any bacteria enfolded by the viscoelastic substance, as compared to conventional systemically or locally applied antibacterial treatments.

No reason exists for making the alleged combination.

The present rejection relies on teachings collected from the Viegas, Chang, and Christ references. However, these three references are not properly combined and cannot establish a case of obviousness as there is no apparent reason evident in the references themselves or based on the general knowledge in the art by which a skilled artisan would combine and modify their teachings as alleged in the rejection. In this case, the present rejection is constructed solely by picking and choosing teachings from the collected references in lieu of any reason as to why a skilled artisan would be led to do so. Without knowledge of the problem identified by Applicant, there is no basis for a skilled artisan to deviate from conventional administration of the viscoelastic substance and a separate antibiotic.

Viegas is provided for teaching a gel composition having an antibacterial substance used as a corneal mask or shield during excimer laser keratectomy or for use as a contact lens. Every instance and example in the Viegas disclosure that relates to ophthalmic applications **involves external use**. The Viegas reference is silent regarding residual traces of viscoelastic substance used within the eye or issues relating to protection and shielding bacteria that are introduced into the eyeball and enfolded within the viscoelastic substance.

Chang is provided for teaching high viscosity compositions used to maintain the corneal dome and protect corneal endothelial cells during intraocular lens implantation surgery. The reference does not teach mixing an antimicrobial or anti-inflammatory agent with the viscous composition. Chang is also silent regarding the problem of enfolding and protecting bacteria.

The Christ reference teaches a method for delivering viscoelastic material into the eye during surgery and then removing the material. However, the reference is silent regarding application of a viscous gel-like composition mixed with an antimicrobial agent into the interior of the eye. The reference also fails to appreciate the problem of enfolding bacteria within the gel.

None of the Viegas, Chang, and Christ references appreciate the particular issues of infection resulting from bacteria enfolded by the viscoelastic gel. Only Applicant's claimed methods afford antimicrobial properties to residual traces of viscoelastic substance left within the eyeball that enfold infectious bacteria introduced during surgery. The present inventive

methods consequently do not shield bacteria from the antimicrobial agent, as is the case with separately administered antibiotics, whether applied systemically (e.g., oral) or locally (e.g., eye drops), as is conventional in the art. Without this knowledge, there is no apparent reason for an eye surgeon to forgo the conventional practice of oral or systemic administration of antibiotics.

The Examiner has not provided any basis as to why a skilled artisan would use the Viegas composition *within* the eye.

Just because the Viegas gel composition could possibly be applied within the eye according to the surgical procedures of Chang or Christ does not establish a case of obviousness. Obviousness requires more – there must be a reason or basis for a person of ordinary skill to make the combination. Absent such a reason, the reference combination is nothing more than a collection of isolated parts constructed using Applicant's claims as a template.

The Examiner substantiates the alleged combination by claiming that "[i]t would have been obvious to use the claimed combination for preserving against ocular infection, considering that preserving against infection is an inherent property of anti-microbial agents." (pp. 4-5 of Office Action dated November 14, 2007.) However, conventional practice in the art also applies an anti-microbial (e.g., antibiotic), albeit systemically or locally. Conventional practice attempts to remove all of the viscoelastic substance after the surgical procedure is complete; **thus, what benefit would possibly be achieved by including an anti-microbial within the viscoelastic gel as it is ordinarily destined to be removed?** Only Applicant has identified that residual traces of the gel can enfold bacteria introduced into the eye and protect these bacteria from contact with systemically or locally administered antibiotics.

Only the present invention recognizes the problem resulting from enfolding introduced bacteria within the viscoelastic substance and provides methods to address the problem.

As illustrated and cited in MPEP § 2141.02, "a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103." *In re Sponnoble*, 405 F.2d 578, 585, 160 USPQ 237, 243 (CCPA 1969) (emphasis in original).

In this case, Applicant has identified a unique mechanism by which internal application of the viscoelastic substance can contribute to post-operative infection. Applicant respectfully directs the Board's and the Examiner's attention to the present application as substantiating evidence for the discovery of the source of the infection problem posed by internal application of a viscoelastic substance. Applicant also submit the publication by Koichiro Tanaka et al., J.

Med. Soc. Toho. Univ., Vol. 52 (5):303-316 (Sept. 2005), submitted with the amendment filed March 13, 2008, as additional support to substantiate Applicant's discovery of this unique problem and the surprising and unexpected results afforded by Applicant's invention. The publication shows: advantages of Antibacterial Visco in preventing infection, that a small number of bacteria can cause infection in the presence of viscoelastic material, and that the use of viscoelastic material makes antibacterial eye drops ineffective by sheltering the bacteria.

Applicant also wishes to direct the Board's and the Examiner's attention to Exhibits A, B, C, and D that were provided with the Amendment filed February 12, 2007 as evidence of secondary considerations that distinguish the present claims from conventional methods. These Exhibits touch on several important Graham Factors, namely unexpected results, long-felt need, and the failure of others. See *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and MPEP § 2141. In particular, the Exhibits contrast the success of Applicant's invention versus the unsatisfactory results or failure of conventional methods that apply a viscoelastic substance and separately apply an antimicrobial agent. Summaries of these exhibits were provided in Applicant's amendment filed August 31, 2007.

CONCLUSION

Applicant respectfully requests that the Board and Examiner reconsider and withdraw the presently outstanding rejection

Respectfully submitted,

Dated: Sept 9, 2008

By: _____

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